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Definitions, adjudication, and reporting of pulmonary embolism-related death in clinical studies: a systematic review

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Definitions of pulmonary embolism-related death

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ABBREVIATIONS

IQR – interquartile range

PE – pulmonary embolism

RCT – randomized clinical trial

VTE – venous thromboembolism

ESSENTIALS

- Pulmonary embolism (PE)-related death is often a component of the outcome venous thromboembolism.
- This systematic review summarizes definitions for PE-related death used in recent studies.
- Only half of the studies reported their definitions for PE-related death, which were heterogeneous.
- PE-related death rates varied widely across studies. A better standardization is needed.

ABSTRACT

BACKGROUND: Pulmonary embolism (PE)-related death is a component of the primary outcome in many venous thromboembolism (VTE) studies. The absence of a standardized definition for PE-related death hampers study outcome evaluation and between-study comparisons.

OBJECTIVES: To summarize definitions for PE-related death used in recent VTE studies and to assess the PE-related death rate.

PATIENTS/METHODS: A systematic literature search was conducted on April 26th, 2018 from January 1st, 2014 up to the search date in MEDLINE, Embase, and CENTRAL. Cohort studies and randomized trials in which PE-related death was included in the primary outcome were eligible. Screening of titles, abstracts, and full-text articles, and data extraction were independently performed in duplicate by two authors. Study outcomes included the definition for PE-related death, VTE case-fatality rate, and death due to PE rate. Descriptive statistics were used to analyze the data.

RESULTS: Of the 6,807 identified citations, 83 studies were included of which 27% were randomized trials, 31% were prospective and 42% retrospective cohort studies. Thirty-five studies (42%) had a central adjudication committee. Thirty-eight (46%) reported a definition for PE-related death of which the most frequently used components were 'autopsy-confirmed PE' (50%), 'objectively confirmed PE before death' (55%), and 'unexplained death' (58%). Median VTE case-fatality rate was 1.8% (interquartile range, 0.0 to 13).

CONCLUSIONS: Only half of the included studies reported definitions for PE-related death, which were very heterogeneous. Case-fatality rate of VTE events varied widely across studies. Standardization of the definition and guidance on adjudication and reporting of PE-related death is needed.

KEYWORDS

Pulmonary embolism

Venous thromboembolism

Cause of Death

Mortality

Outcome Assessment (Health Care)

INTRODUCTION

Pulmonary embolism (PE)-related death is a component of the primary endpoint in many venous thromboembolism (VTE) clinical studies. At present, there is no standardized definition for PE-related death and the use of different definitions across studies may hamper proper trial outcome evaluation and between-study comparisons. In addition, meta-analyses of clinical endpoints including PE-related death may be biased as included studies may report over- or underestimated risk estimates. Central independent adjudication committees are currently suggested by both the Food and Drug Administration and the European Medicine Agency to standardize outcome

assessment, thereby minimizing between-study differences [1,2]. However, recent studies indicated that commonly used definitions of PE-related death may be non-specific despite central adjudication and reproducibility of outcome adjudication for PE-related death appeared to be poor [3,4]. This may lead to misclassifications that significantly affect the validity of study results. In this systematic review, we aimed to summarize definitions for PE-related death used in recent VTE studies and assess the VTE case-fatality rate and death due to PE rate.

METHODS

Literature search

A systematic search of literature was conducted in MEDLINE and Embase on April 26th, 2018 from January 1st, 2014 up to the search date combining terms for 'venous thromboembolism', 'pulmonary embolism', 'deep vein thrombosis', 'fatal', and 'death' (see **Appendix 1** for search strategies). The Cochrane Central Register of Controlled Trials (CENTRAL) was searched from March 1st, 2018 up to the search date.

Eligibility criteria, study selection, and data extraction

Cohort studies and randomized clinical trials (RCTs) in which PE-related death was a component of the primary endpoint were eligible. Studies that were not restricted to adults, those without original data, and conference abstracts were excluded.

Titles, abstracts, and subsequently full-text articles were independently screened in duplicate by two authors (NK and TT) using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). Data extraction was independently performed in duplicate by two authors (NK and TT) using standardized forms, including study characteristics, definitions for PE-related death, and study outcomes (VTE, PE-related death, and all-cause mortality). A discussion was held in case of disagreement in order to reach consensus.

Study outcomes

The primary outcome was the definition for PE-related death used in the included studies. Secondary outcomes were the case-fatality rate of VTE, defined as the proportion of PE-related deaths relative to the total number of VTE events, and the death due to PE rate, defined as the proportion of PE-related deaths relative to the total number of deaths.

Statistical analysis

Descriptive statistics were used to describe study characteristics and definitions for PE-related death. Components of the definitions for PE-related death were reported separately and were categorized into subgroups. The frequency of reported components was presented in a histogram. For each study, the PE-related death rate, the case-fatality rate of VTE events and the death due to PE were computed using reported data on PE-related death, VTE events, and all-cause mortality. In subgroup analyses, each outcome was assessed by study design (i.e., RCT, prospective and retrospective cohort) and by use of a central outcome adjudication committee. All analyses were performed in R (v3.5.1, The R Foundation for Statistical Computing © 2018, www.R-project.org).

RESULTS

Study characteristics

Of the 6,807 citations identified in the literature search, 83 studies were found to be eligible (**Figure 1**; PRISMA flowchart). Characteristics of the included studies are depicted in **Table 1**. Median sample size was 614 (interquartile range [IQR], 212 to 3,289). Twenty-six studies (31%) were prospective, 35 (42%) were retrospective, and 22 (27%) were RCTs. Twenty-three studies (28%) assessed VTE prediction, 19 (23%) prevention, 16 (19%) treatment, 12 (14%) incidence, 5 (6.0%) etiology, 5 (6.0%) were diagnostic studies, and 3 (3.6%) could not be classified into one of these categories. Thirty-five studies (42%) had a central adjudication committee which assessed all outcome events occurring during the study period. Seventeen of 22 RCTs (77%) reported an adjudication committee. These figures were 50% and 14% for prospective and retrospective cohort studies, respectively.

Definitions for pulmonary embolism-related death

Definitions for PE-related death were reported in 38 studies (46%; see **Table 2** for the components of the definitions; see **Appendix 2** for detailed definitions as reported in the original studies). Components of the definition for PE-related death were classified into four categories: 'autopsy-confirmed PE', 'objectively confirmed PE before death', 'unexplained death', and 'other' for those that did not belong to one of the other categories. **Figure 2** depicts the overall frequency of the different components as well as the variety of descriptions used to define these components. 'Autopsy-confirmed PE' was a component of PE-related death in 19 of 38 studies (50%); 'objectively confirmed PE before death' in 21 studies (55%); and 'unexplained death' in 22 studies (58%). Fifteen studies (39%) reported a definition component classified as 'other', including 'objective documentation of PE' for which it was not specified if it regarded objective testing before death or upon autopsy, 'specific signs or symptoms before death in the absence of other (cardiopulmonary) causes of death', and death in which clinical judgment determined whether it was caused by PE. Nine studies (24%) included all three components 'autopsy-confirmed PE', 'objectively confirmed PE before death', and 'unexplained death' in the definition of PE-related death.

Study outcomes

Outcome event rates are detailed in **Table 3**. Pulmonary embolism-related death rates were not reported in 13 studies (16%). The numbers of PE-related deaths objectively confirmed by autopsy or before death were not reported or did not occur in any of the studies. Eleven studies (13%) reported on the number of 'unexplained deaths', accounting for 2.4 to 47% of VTE events.

Median VTE case-fatality rate, defined as the proportion of PE-related deaths relative to the total number of VTE events, was 1.8% (IQR, 0.0 to 13; range, 0.0 to 80; histogram shown in **Appendix 3**). Median VTE case-fatality rate was 0.0% (IQR, 0.0 to 7.1) in RCTs, 11% (IQR, 0.0 to 18) in prospective cohort studies, and 3.8% (IQR, 1.1 to 11) in retrospective cohort studies, respectively.

These figures were 3.6% (IQR, 0.0 to 15) and 1.4% (IQR, 0.0 to 11) in studies with and without an adjudication committee, respectively.

Median proportion of deaths due to PE, defined as the proportion of PE-related deaths relative to the total number of deaths, was 8.2% (IQR, 0.0 to 33; range, 0.0 to 100; histogram shown in **Appendix 4**). Median death due to PE rate was 0.0% (IQR, 0.0 to 13) in RCTs, 7.0% (IQR, 0.0 to 26) in prospective cohort studies, and 33% (IQR, 7.1 to 71) in retrospective cohort studies, respectively. These figures were 6.3% (IQR, 0.0 to 14) and 25.0% (IQR, 1.3 to 67) in studies with and without an adjudication committee, respectively.

DISCUSSION

This systematic review summarizes the definitions for PE-related death reported in recent clinical studies in which PE-related death was a component of the primary outcome. Half of the studies did not report a definition for PE-related death. Definitions used in the remaining studies were heterogeneous, and mostly included the components 'autopsy-confirmed PE', 'objectively confirmed PE before death', or 'unexplained death'. The VTE case-fatality rate and death due to PE rate varied widely among the included studies.

Pulmonary embolism-related death is often a component of the outcome (recurrent) VTE in clinical studies. It is important to realize that the number of deaths classified as being related to PE influences the magnitude of the outcome (recurrent) VTE; studies with higher numbers of PE-related deaths will report higher numbers of (recurrent) VTE events. As mortality rate is often at least as high as the rate of (recurrent) VTE, a high sensitivity and specificity of the definition for PE-related death are crucial to minimize the number of false positive and false negative classifications, which could have deleterious consequences for clinical trial results. In trials with a superiority design, deaths falsely designated as being PE-related can increase the numbers of patients with (recurrent) VTE in both treatment groups, thereby 'diluting' the relative difference and possibly leading to a type II error (failure to reject the null hypothesis when it is false). In those with a non-inferiority

design, a smaller relative difference between groups may lead to a type I error (rejection of the null hypothesis when it is true). For example, the CATCH trial and Hokusai VTE Cancer trial both randomized patients with cancer-associated VTE to two anticoagulant treatment regimens, yet the contribution of PE-related deaths to the primary outcome rate differed widely between the two trials. In the CATCH study, almost half of recurrent VTE events were PE-related deaths, 17 of 31 events (55%) in the tinzaparin treatment arm and 17 of 45 (38%) in the warfarin arm [16]. In the Hokusai VTE Cancer study, these figures were markedly lower: only 3 of 34 recurrent VTE events (8.8%) in the edoxaban group and 3 of 54 events (5.6%) in the dalteparin group werePE-related deaths [17]. CATCH, a superiority trial, reported a non-significant difference in recurrent VTE rates between both treatment arms (hazard ratio, 0.65; 95% CI, 0.41 to 1.03; P=0.07). Hypothetically, if the proportion of PE-related deaths relative to the numbers of recurrent VTE (i.e., the VTE case-fatality rate) would have been comparable to that of the dalteparin arm in Hokusai VTE Cancer (6%), only 15 of 449 patients (3.3%) in the tinzaparin arm would have had recurrent VTE, and 30 of 451 (6.7%) in the warfarin arm. A simple chi-square test indicates that these recurrent VTE rates would have been significantly different (P=0.03).

The accuracy of the definition for PE-related death is highly dependent on the components used to define this outcome. Of the studies that reported a definition for PE-related death, approximately one in two studies included 'autopsy-confirmed PE', 'objectively confirmed PE', or 'unexplained death' as a component of the definition. Only one quarter of these studies included all three components.

Although autopsies are not routinely performed in every deceased patient, it may identify undiagnosed PE. Previous autopsy series in various populations reported that PE was found to be the cause of death in 2.0 to 11% of autopsies [5–9]. As not every PE found at autopsy implies that the patient died from PE, clinical expertise of the pathologist is essential to determine whether the PE may have caused the death.

Objectively confirmed PE before death was considered in half of the definitions for PE-related death. Several descriptions were used to define this component with the aim to more clearly specify when PE diagnosed before death should also be considered to be the cause of death upon adjudication. Some studies added a time frame in which PE had to be diagnosed before death ranging between 5 and 30 days, others indicated that PE had to be clinically severe or that another cause of death should be absent. Regardless of the description used, clinical judgment remains essential to determine whether objectively confirmed PE before death may have substantially contributed to the death of the patient.

Fifty-eight percent of the definitions for PE-related death included unexplained death as a component. As defining unexplained death is challenging, a broad variety of descriptions were used to define this component, including 'unexplained', 'unexpected', and 'sudden' death, and 'death for which PE cannot be ruled out'. The subjective nature of these descriptions may easily lead to misclassification, as previously demonstrated in a study in which the reproducibility of clinical outcome adjudication of a VTE prevention trial was assessed [4]. Of the 179 randomly selected cases, 27 were suspected VTE events of which 8 were classified as 'possible fatal PE' (unexplained death) at repeated adjudication. Of those, 4 were classified as 'other cause of death' in the original trial (50% discordance rate), despite the fact that the same outcome definition (i.e., 'sudden death without an obvious cause') was used for both adjudication sessions. In contrast to VTE research, unexplained deaths in the field of cardiovascular research are regarded as cardiovascular deaths instead of PE-related deaths and thereby contribute to the primary outcome in many trials as well [10–13]. Interestingly, only 3 to 4% of unexplained deaths are found to be caused by PE in unexplained (sudden) death case series [14,15]. Therefore, detailed information on the death circumstances and specific criteria are needed to discriminate between PE and other causes of death.

Rates of PE-related death subcategories were poorly reported or not reported at all. In fact, only 1 in 8 studies reported on the number of unexplained deaths, and PE-related deaths objectively confirmed by autopsy or before death were not reported in most cases or simply did not occur. To facilitate accurate interpretation of study outcomes, reporting on the breakdown of outcome events is important as a high proportion of unexplained deaths could indicate a lack of detailed information on death events. In the abovementioned CATCH and Hokusai VTE Cancer trials, all PE-related deaths were unexplained deaths. Although speculative, one of the reasons for the observed difference in the proportions of PE-related deaths could be the amount and quality of clinical information available for adjudication of these events as study populations were comparable.

The case-fatality rate of (recurrent) VTE events and death due to PE rate varied considerably across studies and appeared not to be influenced by study design or use of an adjudication committee. The most plausible explanation for this is the use of different definitions for PE-related death, but differences in study populations, clinical settings, data collection, follow-up durations, and expertise of adjudication committee members may also have contributed.

Surprisingly, less than half of the studies reported to have an adjudication committee. A previous systematic review reported that 67% of VTE-related RCTs between 2002 and 2012 had an adjudication committee [18]. In the present review of the subsequent years, this proportion moderately increased to 77%, indicating that still 23% of RCTs did not have an adjudication committee (or did not report on it).

Strengths of this study include the broad search strategy and eligibility criteria, which allowed for assessment of PE-related death across a wide range of study types in VTE, thereby representing a comprehensive overview of current practice. The present analysis will be used as the basis for future development of a standardized definition for PE-related death as well as quality improvement recommendations for adjudication of death events in VTE studies.

Subgroup analyses across different study types could not be performed as the number of studies per group was deemed too low, which is a limitation of the study.

In the absence of a standardized definition for PE-related death, study results may be over- or underestimated. As a consequence, internal and external study validity may be affected, and between-study comparability of study results may be suboptimal. Besides the use of a standardized definition for PE-related death, completeness of reporting is also crucial to accurately interpret study results. In particular, the breakdown of PE-related death according to subdefinitions should be reported to balance the proportion of patients with objective documentation of PE before death and those with unexplained death or insufficient information on death circumstances. In addition, systematic use of central independent expert adjudication committees should be advocated to harmonize and standardize outcome assessment. A working group from the Scientific and Standardization Committee on Predictive and Diagnostic Variables in Thrombotic Disease of the International Society on Thrombosis and Haemostasis initiated a project in 2017 with the aim to develop a guidance statement for a standardized definition of PE-related death and recommendations for adjudication and reporting of the cause of death in VTE studies. Use of the proposed standardized definition of PE-related death, adjudication process, and reporting of outcomes will be reassessed several years after publication.

The present systematic review showed that definitions for PE-related death were often not reported in recent VTE studies in which PE-related death was a component of the primary outcome. Reported definitions in the remaining studies were very heterogeneous, adjudication committees were only reported in a selection of studies, and reporting of the breakdown of PE-related death was infrequent, thereby necessitating guidance for a standardized definition, adjudication, and reporting of PE-related death.

REFERENCES

1 Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees [Internet]. U.S. Department of Health and Human Services Food and Drug Administration 2006. Available from: https://www.fda.gov/downloads/regula. 2006.

2 Guideline on data monitoring committees [Internet]. European Medicines Agency. Committee for medicinal products for human use (CHMP) 2005. Available from: https://www.ema.europa.eu/documents/scientific-guideline/guideline-data-monitoring-committees_en.pdf. 2005.

3 Spyropoulos AC, Ageno W, Albers GW, Elliott CG, Halperin JL, Hiatt WR, Maynard GA, Steg PG, Weitz JI, Suh E, Spiro TE, Barnathan ES, Raskob GE, MARINER Investigators. Rivaroxaban for Thromboprophylaxis after Hospitalization for Medical Illness. *N Engl J Med* 2018; **379**: 1118–27.

4 Girard P, Penaloza A, Parent F, Gable B, Sanchez O, Durieux P, Hausfater P, Dambrine S, Meyer G, Roy P-M. Reproducibility of clinical events adjudications in a trial of venous thromboembolism prevention. *J Thromb Haemost* 2017; **15**: 662–9.

5 Sandler DA, Martin JF. Autopsy Proven Pulmonary Embolism in Hospital Patients: Are We Detecting Enough Deep Vein Thrombosis? *J R Soc Med* 1989; **82**: 203–5.

6 Baglin TP, White K, Charles A. Fatal pulmonary embolism in hospitalised medical patients. *J Clin Pathol* 1997; **50**: 609–10.

7 Pineda LA, Hathwar VS, Grant BJB. Clinical Suspicion of Fatal Pulmonary Embolism. *Chest* 2001; **120**: 791–5.

8 Kopcke D, Harryman O, Benbow EW, Hay C, Chalmers N. Mortality from pulmonary embolism is decreasing in hospital patients. *J R Soc Med* 2011; **104**: 327–31.

9 Sweet PH, Armstrong T, Chen J, Masliah E, Witucki P. Fatal pulmonary embolism update: 10 years of autopsy experience at an academic medical center. *JRSM Short Rep* 2013; **4**: 204253331348982.

10 Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS, Widimsky P, Hori M, Avezum A, Piegas LS, Branch KRH, Probstfield J, Bhatt DL, Zhu J, Liang Y, Maggioni AP, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. *N Engl J Med* 2017; **377**: 1319–30.

11 Hiatt WR, Fowkes FGR, Heizer G, Berger JS, Baumgartner I, Held P, Katona BG, Mahaffey KW, Norgren L, Jones WS, Blomster J, Millegård M, Reist C, Patel MR, EUCLID Trial Steering Committee and Investigators. Ticagrelor versus Clopidogrel in Symptomatic Peripheral Artery Disease. *N Engl J Med* 2017; **376**: 32–40.

12 Ridker PM, Revkin J, Amarenco P, Brunell R, Curto M, Civeira F, Flather M, Glynn RJ, Gregoire J, Jukema JW, Karpov Y, Kastelein JJP, Koenig W, Lorenzatti A, Manga P, Masiukiewicz U, Miller M, Mosterd A, Murin J, Nicolau JC, et al. Cardiovascular Efficacy and Safety of Bococizumab in High-Risk Patients. *N Engl J Med* 2017; **376**: 1527–39.

13 Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR, FOURIER Steering Committee and Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med* 2017; **376**: 1713–22.

14 Lucena J, Rico A, Vázquez R, Marín R, Martínez C, Salguero M, Miguel L. Pulmonary embolism and sudden–unexpected death: Prospective study on 2477 forensic autopsies performed at the Institute of Legal Medicine in Seville. *J Forensic Leg Med* 2009; **16**: 196–201.

15 Bougouin W, Marijon E, Planquette B, Karam N, Dumas F, Celermajer DS, Jost D, Lamhaut L, Beganton F, Cariou A, Meyer G, Jouven X. Factors Associated With Pulmonary Embolism-Related Sudden Cardiac Arrest. *Circulation* 2016; **134**: 2125–7.

16 Lee AYY, Kamphuisen PW, Meyer G, Bauersachs R, Janas MS, Jarner MF, Khorana AA. Tinzaparin vs Warfarin for Treatment of Acute Venous Thromboembolism in Patients With Active Cancer. *JAMA* 2015; **314**: 677.

17 Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, Grosso MA, Kakkar AK, Kovacs MJ, Mercuri MF, Meyer G, Segers A, Shi M, Wang T-F, Yeo E, Zhang G, Zwicker JI, Weitz JI, Büller HR, Hokusai VTE Cancer Investigators. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. *N Engl J Med* 2018; **378**: 615–24.

18 Stuck AK, Fuhrer E, Limacher A, Méan M, Aujesky D. Adjudication-related processes are underreported and lack standardization in clinical trials of venous thromboembolism: a systematic review. *J Clin Epidemiol* 2014; **67**: 278–84.

19 Abbasi N, Balayla J, Laporta DP, Kezouh A, Abenhaim HA. Trends, risk factors and mortality among women with venous thromboembolism during labour and delivery: a population-based study of 8 million births. *Arch Gynecol Obstet* 2014; **289**: 275–84.

20 Ageno W, Mantovani LG, Haas S, Kreutz R, Monje D, Schneider J, van Eickels M, Gebel M, Zell E, Turpie AGG. Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study. *Lancet Haematol* 2016; **3**: e12-21.

21 Al-Hameed F, Al-Dorzi HM, Aboelnazer E. The effect of a continuing medical education program on Venous thromboembolism prophylaxis utilization and mortality in a tertiary-care hospital. *Thromb J* 2014; **12**: 9.

22 Rosa-Salazar V, Trujillo-Santos J, Díaz Peromingo JA, Apollonio A, Sanz O, Malý R, Muñoz-Rodriguez FJ, Serrano JC, Soler S, Monreal M. A prognostic score to identify low-risk outpatients with acute deep vein thrombosis in the upper extremity. *J Thromb Haemost* 2015; **13**: 1274–8.

23 Allen C, Seinge R, Maxwell R, Thind D. CT pulmonary angiography and pulmonary embolism following 5809 primary joint arthroplasties. *N Z Med J* 2015; **128**: 41–9.

24 Andreozzi GM, Bignamini AA, Davì G, Palareti G, Matuška J, Holý M, Pawlaczyk-Gabriel K, Džupina A, Sokurenko GY, Didenko YP, Andrei LD, Lessiani G, Visonà A, SURVET Study Investigators. Sulodexide for the Prevention of Recurrent Venous Thromboembolism: The Sulodexide in Secondary Prevention of Recurrent Deep Vein Thrombosis (SURVET) Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. *Circulation* 2015; **132**: 1891–7.

25 Apenteng PN, Hobbs FR, Roalfe A, Muhammad U, Heneghan C, Fitzmaurice D. Incidence of venous thromboembolism in care homes: a prospective cohort study. *Br J Gen Pract* 2017; **67**: e130–7.

26 Assareh H, Chen J, Ou L, Hollis SJ, Hillman K, Flabouris A. Rate of venous thromboembolism among surgical patients in Australian hospitals: a multicentre retrospective cohort study. *BMJ*

Open 2014; **4**: e005502.

27 Bahl V, Shuman AG, Hu HM, Jackson CR, Pannucci CJ, Alaniz C, Chepeha DB, Bradford CR. Chemoprophylaxis for venous thromboembolism in otolaryngology. *JAMA Otolaryngol Head Neck Surg* 2014; **140**: 999–1005.

28 Bayley E, Brown S, Bhamber NS, Howard PW. Fatal pulmonary embolism following elective total hip arthroplasty: a 12-year study. *Bone Joint J* 2016; **98–B**: 585–8.

29 Becattini C, Agnelli G, Lankeit M, Masotti L, Pruszczyk P, Casazza F, Vanni S, Nitti C, Kamphuisen P, Vedovati MC, De Natale MG, Konstantinides S. Acute pulmonary embolism: mortality prediction by the 2014 European Society of Cardiology risk stratification model. *Eur Respir J* 2016; **48**: 780–6.

30 Bedayat A, Sewatkar R, Cai T, George E, Imanzadeh A, Hussain Z, Dunne RM, Hunsaker AR, Rybicki FJ, Kumamaru KK. Association Between Confidence Level of Acute Pulmonary Embolism Diagnosis on CTPA images and Clinical Outcomes. *Acad Radiol* 2015; **22**: 1555–61.

31 Blix K, Gran O V, Severinsen MT, Cannegieter SC, Jensvoll H, Overvad K, Hammerstrøm J, Tjønneland A, Naess IA, Braekkan SK, Rosendaal FR, Kristensen SR, Hansen J-B. Impact of time since diagnosis and mortality rate on cancer-associated venous thromboembolism: the Scandinavian Thrombosis and Cancer (STAC) cohort. *J Thromb Haemost* 2018; **16**: 1327–35.

32 Bogdan Y, Tornetta P, Leighton R, Dahn U, Sagi H, Nalley C, Sanders D, Siegel J, Mullis B, Bemenderfer T, Vallier H, Boyd A, Schmidt A, Westberg JR, Egol KA, Kottmeier S, Collinge C. Treatment and complications in orthopaedic trauma patients with symptomatic pulmonary embolism. *J Orthop Trauma* 2014; **28 Suppl 1**: S6-9.

33 Bouras G, Burns EM, Howell A-M, Bottle A, Athanasiou T, Darzi A. Risk of Post-Discharge Venous Thromboembolism and Associated Mortality in General Surgery: A Population-Based Cohort Study Using Linked Hospital and Primary Care Data in England. *PLoS One* 2015; **10**: e0145759.

34 Bova C, Vanni S, Prandoni P, Morello F, Dentali F, Bernardi E, Mumoli N, Bucherini E, Barbar S, Picariello C, Enea I, Pesavento R, Bottino F, Jiménez D, Bova Score Validation Study Investigators. A prospective validation of the Bova score in normotensive patients with acute pulmonary embolism. *Thromb Res* 2018; **165**: 107–11.

35 Büller HR, Bethune C, Bhanot S, Gailani D, Monia BP, Raskob GE, Segers A, Verhamme P, Weitz JI, FXI-ASO TKA Investigators. Factor XI antisense oligonucleotide for prevention of venous thrombosis. *N Engl J Med* 2015; **372**: 232–40.

36 Camporese G, Bernardi E, Noventa F, Bosco M, Monteleone G, Santoro L, Bortoluzzi C, Freguja S, Nardin M, Marullo M, Zanon G, Mazzola C, Damiani G, Maniscalco P, Imberti D, Lodigiani C, Becattini C, Tonello C, Agnelli G, ERIKA Study Group. Efficacy of Rivaroxaban for thromboprophylaxis after Knee Arthroscopy (ERIKA). A phase II, multicentre, double-blind, placebo-controlled randomised study. *Thromb Haemost* 2016; **116**: 349–55.

37 Catterick D, Hunt BJ. Impact of the national venous thromboembolism risk assessment tool in secondary care in England: retrospective population-based database study. *Blood Coagul Fibrinolysis* 2014; **25**: 571–6.

38 Ciurzyński M, Kurnicka K, Lichodziejewska B, Kozłowska M, Pływaczewska M, Sobieraj P, Dzikowska-Diduch O, Goliszek S, Bienias P, Kostrubiec M, Pruszczyk P. Tricuspid Regurgitation Peak Gradient (TRPG)/Tricuspid Annulus Plane Systolic Excursion (TAPSE) — A Novel

Parameter for Stepwise Echocardiographic Risk Stratification in Normotensive Patients With Acute Pulmonary Embolism —. *Circ J* 2018; **82**: 1179–85.

39 Cohen AT, Harrington RA, Goldhaber SZ, Hull RD, Wiens BL, Gold A, Hernandez AF, Gibson CM. Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients. *N Engl J Med* 2016; **375**: 534–44.

40 Couturaud F, Sanchez O, Pernod G, Mismetti P, Jego P, Duhamel E, Provost K, dit Sollier CB, Presles E, Castellant P, Parent F, Salaun P-Y, Bressollette L, Nonent M, Lorillon P, Girard P, Lacut K, Guégan M, Bosson J-L, Laporte S, et al. Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism. *Jama* 2015; **314**: 31.

41 den Exter PL, Zondag W, Klok FA, Brouwer RE, Dolsma J, Eijsvogel M, Faber LM, van Gerwen M, Grootenboers MJ, Heller-Baan R, Hovens MM, Jonkers GJPM, van Kralingen KW, Melissant CF, Peltenburg H, Post JP, van de Ree MA, Vlasveld LTT, de Vreede MJ, Huisman M V, et al. Efficacy and Safety of Outpatient Treatment Based on the Hestia Clinical Decision Rule with or without N-Terminal Pro-Brain Natriuretic Peptide Testing in Patients with Acute Pulmonary Embolism. A Randomized Clinical Trial. *Am J Respir Crit Care Med* 2016; **194**: 998–1006.

42 Etesamifard N, Shirani S, Jenab Y, Lotfi-Tokaldany M, Pourjafari M, Jalali A. Role of clinical and pulmonary computed tomography angiographic parameters in the prediction of short- and long-term mortality in patients with pulmonary embolism. *Intern Emerg Med* 2016; **11**: 405–13.

43 Fernández C, Bova C, Sanchez O, Prandoni P, Lankeit M, Konstantinides S, Vanni S, Fernández-Golfín C, Yusen RD, Jiménez D. Validation of a Model for Identification of Patients at Intermediate to High Risk for Complications Associated With Acute Symptomatic Pulmonary Embolism. *Chest* 2015; **148**: 211–8.

44 Font C, Carmona-Bayonas A, Fernández-Martinez A, Beato C, Vargas A, Gascon P, Otero R. Outpatient management of pulmonary embolism in cancer: data on a prospective cohort of 138 consecutive patients. *J Natl Compr Canc Netw* 2014; **12**: 365–73.

45 Freund Y, Cachanado M, Aubry A, Orsini C, Raynal P-A, Féral-Pierssens A-L, Charpentier S, Dumas F, Baarir N, Truchot J, Desmettre T, Tazarourte K, Beaune S, Leleu A, Khellaf M, Wargon M, Bloom B, Rousseau A, Simon T, Riou B. Effect of the Pulmonary Embolism Rule-Out Criteria on Subsequent Thromboembolic Events Among Low-Risk Emergency Department Patients. *JAMA* 2018; **319**: 559.

46 Gaertner S, Cordeanu E-M, Nouri S, Faller A-M, Frantz A-S, Mirea C, Bilbault P, Ohlmann P, Le Ray I, Stephan D. Rivaroxaban versus standard anticoagulation for symptomatic venous thromboembolism (REMOTEV observational study): Analysis of 6-month outcomes. *Int J Cardiol* 2017; **226**: 103–9.

47 George E, Kumamaru KK, Ghosh N, Gonzalez Quesada C, Wake N, Bedayat A, Dunne RM, Saboo SS, Khandelwal A, Hunsaker AR, Rybicki FJ, Gerhard-Herman M. Computed tomography and echocardiography in patients with acute pulmonary embolism: part 2: prognostic value. *J Thorac Imaging* 2014; **29**: W7-12.

48 Gladman M, Dehaan M, Pinto H, Geerts W, Zinman L. Venous thromboembolism in amyotrophic lateral sclerosis: a prospective study. *Neurology* 2014; **82**: 1674–7.

49 Hara N, Miyamoto T, Iwai T, Yamaguchi J, Hijikata S, Watanabe K, Sagawa Y, Masuda R, Miyazaki R, Miwa N, Sekigawa M, Yamaguchi T, Nagata Y, Nozato T, Obayashi T. Assessment

of the Safety and Efficacy of Edoxaban for the Treatment of Venous Thromboembolism Secondary to Active Malignancy. *Ann Vasc Dis* 2017; **10**: 407–10.

50 Horner D, Hogg K, Body R, Jones S, Nash MJ, Mackway-Jones K. Single whole-leg compression ultrasound for exclusion of deep vein thrombosis in symptomatic ambulatory patients: a prospective observational cohort study. *Br J Haematol* 2014; **164**: 422–30.

51 Horner D, Hogg K, Body R, Nash MJ, Baglin T, Mackway-Jones K. The Anticoagulation of Calf Thrombosis (ACT) Project. *Chest* 2014; **146**: 1468–77.

52 Im DJ, Hur J, Han KH, Lee H-J, Kim YJ, Kwon W, Choi BW. Acute Pulmonary Embolism: Retrospective Cohort Study of the Predictive Value of Perfusion Defect Volume Measured With Dual-Energy CT. *Am J Roentgenol* 2017; **209**: 1015–22.

53 Imberti D, Baldini E, Pierfranceschi MG, Nicolini A, Cartelli C, De Paoli M, Boni M, Filippucci E, Cariani S, Bottani G. Prophylaxis of Venous Thromboembolism with Low Molecular Weight Heparin in Bariatric Surgery: a Prospective, Randomised Pilot Study Evaluating Two Doses of Parnaparin (BAFLUX Study). *Obes Surg* 2014; **24**: 284–91.

54 Izumi M, Migita K, Nakamura M, Jiuchi Y, Sakai T, Yamaguchi T, Asahara T, Nishino Y, Bito S, Miyata S, Kumagai K, Osaki M, Mawatari M, Motokawa S. Risk of Venous Thromboembolism after Total Knee Arthroplasty in Patients with Rheumatoid Arthritis. *J Rheumatol* 2015; **42**: 928–34.

55 Jiménez-Alcázar M, Limacher A, Panda R, Méan M, Bitterling J, Peine S, Renné T, Beer JH, Aujesky D, Lämmle B, Fuchs TA. Circulating extracellular DNA is an independent predictor of mortality in elderly patients with venous thromboembolism. Garcia de Frutos P, editor. *PLoS One* 2018; **13**: e0191150.

56 Johansson M, Lind M, Jansson J-H, Fhärm E, Johansson L. Fasting plasma glucose, oral glucose tolerance test, and the risk of first-time venous thromboembolism. A report from the VEINS cohort study. *Thromb Res* 2018; **165**: 86–94.

57 Kawaguchi R, Haruta S, Kobayashi H. Efficacy and safety of venous thromboembolism prophylaxis with fondaparinux in women at risk after cesarean section. *Obstet Gynecol Sci* 2017; **60**: 535.

58 Kline JA, Nordenholz KE, Courtney DM, Kabrhel C, Jones AE, Rondina MT, Diercks DB, Klinger JR, Hernandez J. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. *J Thromb Haemost* 2014; **12**: 459–68.

59 Koć M, Kostrubiec M, Elikowski W, Meneveau N, Lankeit M, Grifoni S, Kuch-Wocial A, Petris A, Zaborska B, Stefanović BS, Hugues T, Torbicki A, Konstantinides S, Pruszczyk P. Outcome of patients with right heart thrombi: the Right Heart Thrombi European Registry. *Eur Respir J* 2016; **47**: 869–75.

60 Kolluri R, Plessa AL, Sanders MC, Singh NK, Lucore C. A randomized study of the safety and efficacy of fondaparinux versus placebo in the prevention of venous thromboembolism after coronary artery bypass graft surgery. *Am Heart J* 2016; **171**: 1–6.

61 Krause M, Henningsen A, Torge A, Juhl D, Junker R, Kenet G, Kowalski D, Limperger V, Mesters R, Anonymous, Rocke A, Shneyder M, Clausnizer H, Schiesewitz H, Nowak-Göttl U. Impact of gender on safety and efficacy of Rivaroxaban in adolescents & young adults with venous thromboembolism. *Thromb Res* 2016; **148**: 145–51.

62 Kumamaru KK, George E, Ghosh N, Quesada CG, Wake N, Gerhard-Herman M, Rybicki FJ. Normal ventricular diameter ratio on CT provides adequate assessment for critical right ventricular strain among patients with acute pulmonary embolism. *Int J Cardiovasc Imaging* 2016; **32**: 1153–61.

63 Lankeit M, Jimenez D, Kostrubiec M, Dellas C, Kuhnert K, Hasenfuss G, Pruszczyk P, Konstantinides S. Validation of N-terminal pro-brain natriuretic peptide cut-off values for risk stratification of pulmonary embolism. *Eur Respir J* 2014; **43**: 1669–77.

64 Lee AYY, Kamphuisen PW, Meyer G, Bauersachs R, Janas MS, Jarner MF, Khorana AA. Tinzaparin vs Warfarin for Treatment of Acute Venous Thromboembolism in Patients With Active Cancer. *JAMA* 2015; **314**: 677.

65 Li C, Lin CT, Kligerman SJ, Hong SN, White CS. Enhancement Characteristics of the Computed Tomography Pulmonary Angiography Test Bolus Curve and Its Use in Predicting Right Ventricular Dysfunction and Mortality in Patients With Acute Pulmonary Embolism. *J Thorac Imaging* 2015; **30**: 274–81.

66 Marconi L, Carrozzi L, Aquilini F, Celi A, Pistelli F, Palla A. Five-year follow-up of pulmonary embolism under anticoaugulation. *Medicine (Baltimore)* 2016; **95**: e4364.

67 Migita K, Bito S, Nakamura M, Miyata S, Saito M, Kakizaki H, Nakayama Y, Matsusita T, Furuichi I, Sasazaki Y, Tanaka T, Yoshida M, Kaneko H, Abe I, Mine T, Ihara K, Kuratsu S, Saisho K, Miyahara H, Segata T, et al. Venous thromboembolism after total joint arthroplasty: results from a Japanese multicenter cohort study. *Arthritis Res Ther* 2014; **16**: R154.

68 Mismetti P, Laporte S, Pellerin O, Ennezat P-V, Couturaud F, Elias A, Falvo N, Meneveau N, Quere I, Roy P-M, Sanchez O, Schmidt J, Seinturier C, Sevestre M-A, Beregi J-P, Tardy B, Lacroix P, Presles E, Leizorovicz A, Decousus H, et al. Effect of a Retrievable Inferior Vena Cava Filter Plus Anticoagulation vs Anticoagulation Alone on Risk of Recurrent Pulmonary Embolism. *JAMA* 2015; **313**: 1627.

69 Moores L, Kline J, Portillo AK, Resano S, Vicente A, Arrieta P, Corres J, Tapson V, Yusen RD, Jiménez D. Multidetector computed tomographic pulmonary angiography in patients with a high clinical probability of pulmonary embolism. *J Thromb Haemost* 2016; **14**: 114–20.

70 Mos ICM, Douma RA, Erkens PMG, Kruip MJHA, Hovens MM, van Houten AA, Hofstee HMA, Kooiman J, Klok FA, Büller HR, Kamphuisen PW, Huisman M V., Prometheus Study Group. Diagnostic outcome management study in patients with clinically suspected recurrent acute pulmonary embolism with a structured algorithm. *Thromb Res* Elsevier Ltd; 2014; **133**: 1039–44.

71 Nendaz M, Spirk D, Kucher N, Aujesky D, Hayoz D, Beer J, Husmann M, Frauchiger B, Korte W, Wuillemin W, Jäger K, Righini M, Bounameaux H. Multicentre validation of the Geneva Risk Score for hospitalised medical patients at risk of venous thromboembolism. *Thromb Haemost* 2014; **111**: 531–8.

72 Obi AT, Pannucci CJ, Nackashi A, Abdullah N, Alvarez R, Bahl V, Wakefield TW, Henke PK. Validation of the Caprini Venous Thromboembolism Risk Assessment Model in Critically Ill Surgical Patients. *JAMA Surg* 2015; **150**: 941.

73 Ogonda L, Hill J, Doran E, Dennison J, Stevenson M, Beverland D. Aspirin for thromboprophylaxis after primary lower limb arthroplasty: early thromboembolic events and 90 day mortality in 11,459 patients. *Bone Joint J* 2016; **98–B**: 341–8.

74 Onundarson PT, Francis CW, Indridason OS, Arnar DO, Bjornsson ES, Magnusson MK, Juliusson SJ, Jensdottir HM, Vidarsson B, Gunnarsson PS, Lund SH, Gudmundsdottir BR. Fiix-prothrombin time versus standard prothrombin time for monitoring of warfarin anticoagulation: a single centre, double-blind, randomised, non-inferiority trial. *Lancet Haematol* 2015; **2**: e231–40.

75 Paczyńska M, Sobieraj P, Burzyński Ł, Kostrubiec M, Wiśniewska M, Bienias P, Kurnicka K, Lichodziejewska B, Pruszczyk P, Ciurzyński M. Tricuspid annulus plane systolic excursion (TAPSE) has superior predictive value compared to right ventricular to left ventricular ratio in normotensive patients with acute pulmonary embolism. *Arch Med Sci* 2016; **5**: 1008–14.

76 Pruszczyk P, Goliszek S, Lichodziejewska B, Kostrubiec M, Ciurzyński M, Kurnicka K, Dzikowska-Diduch O, Palczewski P, Wyzgal A. Prognostic Value of Echocardiography in Normotensive Patients With Acute Pulmonary Embolism. *JACC Cardiovasc Imaging* 2014; **7**: 553–60.

77 Ratib S, Walker AJ, Card TR, Grainge MJ. Risk of venous thromboembolism in hospitalised cancer patients in England—a cohort study. *J Hematol Oncol* 2016; **9**: 60.

78 Reitter E-M, Kaider A, Ay C, Quehenberger P, Marosi C, Zielinski C, Pabinger I. Longitudinal analysis of hemostasis biomarkers in cancer patients during antitumor treatment. *J Thromb Haemost* 2016; **14**: 294–305.

79 Roy P-M, Corsi DJ, Carrier M, Theogene A, de Wit C, Dennie C, Le Gal G, Delluc A, Moumneh T, Rodger M, Wells P, Gandara E. Net clinical benefit of hospitalization versus outpatient management of patients with acute pulmonary embolism. *J Thromb Haemost* 2017; **15**: 685–94.

80 Roy P-M, Rachas A, Meyer G, Le Gal G, Durieux P, El Kouri D, Honnart D, Schmidt J, Legall C, Hausfater P, Chrétien J-M, Mottier D. Multifaceted Intervention to Prevent Venous Thromboembolism in Patients Hospitalized for Acute Medical Illness: A Multicenter Cluster-Randomized Trial. ten Cate H, editor. *PLoS One* 2016; **11**: e0154832.

81 Ryan SP, Mayerson JL, Crist MK, Scharschmidt TJ. Inferior vena cava filter and aspirin in thromboprophylaxis during resection of pelvic malignancies. *Curr Orthop Pract* 2015; **26**: 314–7.

82 Sakai T, Izumi M, Kumagai K, Kidera K, Yamaguchi T, Asahara T, Kozuru H, Jiuchi Y, Mawatari M, Osaki M, Motokawa S, Migita K. Effects of a Foot Pump on the Incidence of Deep Vein Thrombosis After Total Knee Arthroplasty in Patients Given Edoxaban: A Randomized Controlled Study. *Medicine (Baltimore)* 2016; **95**: e2247.

83 Samama CM, Lecoules N, Kierzek G, Claessens YE, Riou B, Rosencher N, Mismetti P, Sautet A, Barrellier M-T, Apartsin K, Jonas M, Caeiro JR, Van der veen AH, Roy P-M. Étude comparant le fondaparinux à une héparine de bas poids moléculaire dans la prévention de la maladie thromboembolique veineuse en cas d'immobilisation rigide ou semi-rigide après traumatisme isolé non chirurgical du membre inférieur au-dessous du geno. *Ann françaises médecine d'urgence* 2014; .

84 Selby R, Geerts WH, Kreder HJ, Crowther MA, Kaus L, Sealey F. Symptomatic Venous Thromboembolism Uncommon without Thromboprophylaxis After Isolated Lower-Limb Fracture. *J Bone Jt Surg* 2014; **96**: e83.

85 Selby R, Geerts WH, Kreder HJ, Crowther MA, Kaus L, Sealey F. A Double-Blind, Randomized

Controlled Trial of the Prevention of Clinically Important Venous Thromboembolism After Isolated Lower Leg Fractures. *J Orthop Trauma* 2015; **29**: 224–30.

86 Shirakawa T, Iso H, Yamagishi K, Yatsuya H, Tanabe N, Ikehara S, Ukawa S, Tamakoshi A. Watching Television and Risk of Mortality From Pulmonary Embolism Among Japanese Men and Women. *Circulation* 2016; **134**: 355–7.

87 Suttorp MM, Hoekstra T, Ocak G, van Diepen ATN, Ott I, Mittelman M, Rabelink TJ, Krediet RT, Dekker FW. Erythropoiesis-stimulating agents and thrombotic events in dialysis patients. *Thromb Res* 2014; **134**: 1081–6.

88 Tafur A, Caprini J, Cote L, Trujillo-Santos J, Del Toro J, Garcia-Bragado F, Tolosa C, Barillari G, Visona A, Monreal M. Predictors of active cancer thromboembolic outcomes. *Thromb Haemost* 2017; **117**: 1192–8.

89 Tanaka H, Katsuragi S, Osato K, Hasegawa J, Nakata M, Murakoshi T, Yoshimatsu J, Sekizawa A, Kanayama N, Ishiwata I, Ikeda T. Increase in maternal death-related venous thromboembolism during pregnancy in Japan (2010-2013). *Circ J* 2015; **79**: 1357–62.

90 Tapson VF, Hazelton JP, Myers J, Robertson C, Gilani R, Dunn JA, Bukur M, Croce MA, Peick A, West S, Lottenberg L, Doucet J, Miller PR, Crookes B, Gandhi RR, Croft CA, Manasia A, Hoey BA, Lieberman H, Guillamondegui OD, et al. Evaluation of a Device Combining an Inferior Vena Cava Filter and a Central Venous Catheter for Preventing Pulmonary Embolism Among Critically Ill Trauma Patients. *J Vasc Interv Radiol* 2017; **28**: 1248–54.

91 Twig G, Ben-Ami Shor D, Furer A, Levine H, Derazne E, Goldberger N, Haklai Z, Levy M, Afek A, Leiba A, Kark JD. Adolescent Body Mass Index and Cardiovascular Disease–Specific Mortality by Midlife. *J Clin Endocrinol Metab* 2017; **102**: 3011–20.

92 van Adrichem RA, Nemeth B, Algra A, le Cessie S, Rosendaal FR, Schipper IB, Nelissen RGHH, Cannegieter SC. Thromboprophylaxis after Knee Arthroscopy and Lower-Leg Casting. *N Engl J Med* 2017; **376**: 515–25.

93 van der Hulle T, Cheung WY, Kooij S, Beenen LFM, van Bemmel T, van Es J, Faber LM, Hazelaar GM, Heringhaus C, Hofstee H, Hovens MMC, Kaasjager KAH, van Klink RCJ, Kruip MJHA, Loeffen RF, Mairuhu ATA, Middeldorp S, Nijkeuter M, van der Pol LM, Schol-Gelok S, et al. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. *Lancet* 2017; **390**: 289–97.

94 van Es N, Louzada M, Carrier M, Tagalakis V, Gross PL, Shivakumar S, Rodger MA, Wells PS. Predicting the risk of recurrent venous thromboembolism in patients with cancer: A prospective cohort study. *Thromb Res* 2018; **163**: 41–6.

95 Vanni S, Jimenez D, Nazerian P, Morello F, Parisi M, Daghini E, Pratesi M, Lopez R, Bedate P, Lobo JL, Jara-Palomares L, Portillo AK, Grifoni S. Short-term clinical outcome of normotensive patients with acute PE and high plasma lactate. *Thorax* 2015; **70**: 333–8.

96 Wahlsten LR, Eckardt H, Lyngbæk S, Jensen PF, Fosbøl EL, Torp-Pedersen C, Gislason GH, Olesen JB. Symptomatic Venous Thromboembolism Following Fractures Distal to the Knee. *J Bone Jt Surg* 2015; **97**: 470–7.

97 Walker AJ, Baldwin DR, Card TR, Powell HA, Hubbard RB, Grainge MJ. Risk of venous thromboembolism in people with lung cancer: a cohort study using linked UK healthcare data. *Br J Cancer* 2016; **115**: 115–21.

98 Weitz JI, Lensing AWA, Prins MH, Bauersachs R, Beyer-Westendorf J, Bounameaux H, Brighton TA, Cohen AT, Davidson BL, Decousus H, Freitas MCS, Holberg G, Kakkar AK, Haskell L, van Bellen B, Pap AF, Berkowitz SD, Verhamme P, Wells PS, Prandoni P. Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism. *N Engl J Med* 2017; **376**: 1211–22.

99 Yamada N, Hirayama A, Maeda H, Sakagami S, Shikata H, Prins MH, Lensing AW, Kato M, Onuma J, Miyamoto Y, Iekushi K, Kajikawa M. Oral rivaroxaban for Japanese patients with symptomatic venous thromboembolism – the J-EINSTEIN DVT and PE program. *Thromb J* 2015; **13**: 2.

100 Zahir MN, Shaikh Q, Shabbir-Moosajee M, Jabbar AA. Incidence of Venous Thromboembolism in cancer patients treated with Cisplatin based chemotherapy - a cohort study. *BMC Cancer* 2017; **17**: 57.

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TABLES

Table 1 – Study characteristics

Study	Sample size	Design	Centers	Study type	Primary outcome	Adjudication committee
Abbasi, 2011 [19]	8,826,439	Retrospective cohort	Multi-center	Etiology	VTE in pregnancy and maternal mortality from VTE	No
Ageno, 2016 [20]	5,142	Prospective cohort	Multi-center	Treatment	Symptomatic recurrent VTE, major bleeding, all-cause mortality	Yes
Al-Hameed, 2014 [21]	147	Retrospective cohort	Single center	Prevention	VTE prophylaxis and VTE-related in-hospital mortality.	No
Alatri, 2017 [22]	383	Prospective cohort	Multi-center	Prediction	Recurrent VTE, fatal VTE, major bleeding, and overall mortality.	No
Allen, 2015 [23]	5,809	Retrospective cohort	Multi-center	Incidence	PE and PE-related mortality	No
Andreozzi, 2015 [24]	617	RCT	Multi-center	Treatment	Recurrent VTE and major bleeding and clinically relevant non-major bleeding	Yes
Apenteng, 2017 [25]	1,011	Retrospective cohort	Multi-center	Incidence	VTE	Yes
Assareh, 2014 [26]	4,223,317	Retrospective cohort	Multi-center	Incidence	Recurrent VTE and all-cause mortality	No
Bahl, 2014 [27]	3,498	Retrospective cohort	Single center	Prevention	VTE and major bleeding	No
Bayley, 2016 [28]	7,983	Retrospective cohort	Single center	Prevention	Fatal PE	No
Becattini, 2016 [29]	906	Prospective cohort	Multi-center	Prediction	Death and PE-related death	No
Bedayat, 2015 [30]	1,664	Retrospective cohort	Single center	Prediction	PE-related mortality	Yes

Study	Sample size	Design	Centers	Study type	Primary outcome	Adjudication committee
Blix, 2018 [31]	14,272	Retrospective cohort	Multi-center	Incidence	VTE	No
Bogdan, 2014 [32]	312	Retrospective cohort	Multi-center	Incidence	Recurrent VTE, death from PE and improvement in vitals or symptoms at discharge	No
Bouras, 2015 [33]	159,039	Retrospective cohort	Multi-center	Incidence	VTE and VTE-related mortality	No
Bova, 2018 [34]	639	Prospective cohort	Multi-center	Prediction	PE-related death, hemodynamic collapse, and recurrent non-fatal PE	No
Büller, 2015 [35]	300	RCT	Multi-center	Prevention	VTE	Yes
Camporese, 2016 [36]	241	RCT	Multi-center	Prevention	All-cause mortality, symptomatic VTE, and asymptomatic proximal DVT	No
Catterick, 2014 [37]	-	Retrospective cohort	Multi-center	Other	VTE, VTE-related mortality, VTE-related secondary diagnosis rates, readmission rates and mortality rates	No
Ciurzynski, 2018 [38]	400	Retrospective cohort	Single center	Prediction	PE-related death and/or rescue thrombolysis	No
Cohen, 2016 [39]	7,513	RCT	Multi-center	Prevention	VTE, and major bleeding	Yes
Couturaud, 2015 [40]	371	RCT	Multi-center	Treatment	Recurrent VTE and major bleeding	Yes
Den Exter, 2016 [41]	550	RCT	Multi-center	Treatment	PE related mortality, major bleeding related mortality, cardiopulmonary resuscitation, admission to an Intensive Care Unit, or requirement of thrombolytic therapy or surgical embolectomy.	Yes
Etesamifard, 2016 [42]	203	Retrospective cohort	Single center	Prediction	PE-related death, 30-day complications, and all-cause mortality	No

Study	Sample size	Design	Centers	Study type	Primary outcome	Adjudication committee
Fernandez, 2015 [43]	1,083	Retrospective cohort	Single center	Prediction	Death from PE, hemodynamic collapse, or recurrent nonfatal PE	No
Font, 2014 [44]	138	Prospective cohort	Single center	Treatment	All-cause mortality and PE-related mortality	Yes
Freund, 2018 [45]	1,916	RCT	Multi-center	Diagnosis	VTE	Yes
Gaertner, 2017 [46]	499	Prospective cohort	Single center	Treatment	Recurrent VTE, major and non-major clinically relevant bleeding, major adverse cardiovascular events and death	No
George, 2014 [47]	785	Retrospective cohort	Single center	Prediction	PE-related death	Yes
Gladman, 2014 [48]	50	Prospective cohort	Single center	Etiology	VTE	No
Hara, 2017 [49]	53	Retrospective cohort	Single center	Treatment	Recurrent VTE and VTE-related mortality	No
Horner, 2014 [50]	212	Prospective cohort	Single center	Diagnosis	VTE and VTE-related death	Yes
Horner, 2014 [51]	70	RCT	Single center	Treatment	Proximal propagation of distal DVT, PE, VTE-related sudden death or major bleeding	No
Im, 2017 [52]	172	Retrospective cohort	Single center	Prediction	All-cause mortality and PE-related death	No
Imberti, 2014 [53]	258	RCT	Multi-center	Prevention	VTE, major bleeding and clinically relevant nonmajor bleeding, and all-cause mortality.	Yes
Izumi, 2015 [54]	1,288	Prospective cohort	Multi-center	Incidence	VTE	No
Jimenez-Alcazar, 2018 [55]	611	Prospective cohort	Multi-center	Prediction	Recurrent VTE	Yes
Johansson, 2018 [56]	108,025	Retrospective cohort	Multi-center	Prediction	VTE	No

Study	Sample size	Design	Centers	Study type	Primary outcome	Adjudication committee
Kawaguchi, 2017 [57]	295	Retrospective cohort	Single center	Prevention	VTE and VTE-related death	No
Kline, 2014 [58]	83	RCT	Multi-center	Treatment	Death from PE, circulatory shock, or need for intubation. Death from hemorrhage, and bleeding.	No
Koc, 2016 [59]	138	Retrospective cohort	Multi-center	Prediction	PE-related mortality	No
Kolluri, 2016 [60]	78	RCT	Single center	Prevention	VTE and major bleeding	No
Krause, 2016 [61]	212	Prospective cohort	Multi-center	Treatment	VTE, thrombus progression during treatment, VTE-related death, and bleeding	No
Kumamaru, 2016 [62]	579	Retrospective cohort	Single center	Prediction	PE-related mortality	No
Lankeit, 2014 [63]	688	Prospective cohort	Multi-center	Prediction	PE-related death and PE-related complications	No
Lee, 2015 [64]	900	RCT	Multi-center	Treatment	VTE, major bleeding, clinically relevant nonmajor bleeding, and all-cause mortality	Yes
Li, 2015 [65]	71	Retrospective cohort	Single center	Prediction	PE-related mortality	No
Marconi, 2016 [66]	471	Prospective cohort	Single center	Treatment	Recurrent VTE	No
Migita, 2014 [67]	2,162	Prospective cohort	Multi-center	Prevention	VTE	No
Mismetti, 2015 [68]	399	RCT	Multi-center	Treatment	Recurrent PE	Yes
Moores, 2016 [69]	134	Prospective cohort	Single center	Diagnosis	VTE	Yes
Mos, 2014 [70]	516	Prospective cohort	Multi-center	Diagnosis	Recurrent VTE	Yes

Study	Sample size	Design	Centers	Study type	Primary outcome	Adjudication committee
Nendaz, 2014 [71]	1,478	Prospective cohort	Multi-center	Prediction	VTE and VTE-related death	Yes
Obi, 2015 [72]	4,844	Retrospective cohort	Single center	Prediction	VTE	No
Ogonda, 2016 [73]	11,459	Retrospective cohort	Multi-center	Prevention	Fatal PE	No
Onundarson, 2015 [74]	1,156	RCT	Single center	Other	Non-fatal and fatal arterial or venous thromboembolism	Yes
Paczynska, 2016 [75]	76	Prospective cohort	Single center	Prediction	PE-related mortality	No
Pruszczyk, 2014 [76]	411	Prospective cohort	Single center	Prediction	PE-related mortality and rescue thrombolysis	No
Raskob, 2018 [17]	1,050	RCT	Multi-center	Treatment	Recurrent VTE and major bleeding.	Yes
Ratib, 2016 [77]	3,558,680	Retrospective cohort	Multi-center	Incidence	VTE	No
Reitter, 2016 [78]	112	Prospective cohort	Single center	Prediction	VTE	Yes
Roy, 2017 [79]	1,081	Retrospective cohort	Single center	Other	Recurrent VTE, PE-related death, major bleeding, and all-cause mortality	Yes
Roy, 2016 [80]	15,351	RCT	Multi-center	Prevention	VTE, major bleeding, and sudden death with no obvious cause	Yes
Ryan, 2015 [81]	24	Retrospective cohort	Single center	Prevention	VTE	No
Sakai, 2016 [82]	120	RCT	Single center	Prevention	VTE	No
Samama, 2014 [83]	1,349	RCT	Multi-center	Prevention	VTE and death	Yes

Study	Sample size	Design	Centers	Study type	Primary outcome	Adjudication committee
Selby, 2014 [84]	1,200	Prospective cohort	Multi-center	Prevention	VTE	Yes
Selby, 2015 [85]	265	RCT	Multi-center	Prevention	VTE	Yes
Shirakawa, 2016 [86]	86,024	Retrospective cohort	Multi-center	Etiology	PE-related mortality	No
Suttorp, 2014 [87]	805	Retrospective cohort	Multi-center	Etiology	Fatal and non-fatal thrombotic events	No
Tafur, 2017 [88]	7,948	Prospective cohort	Multi-center	Prediction	Recurrent VTE, major bleeding, and all-cause mortality	No
Tanaka, 2015 [89]	184	Retrospective cohort	Multi-center	Incidence	Maternal-death-related VTE	Yes
Tapson, 2017 [90]	163	Prospective cohort	Multi-center	Prevention	Clinically significant PE or fatal PE	Yes
Twig, 2017 [91]	2,294,139	Retrospective cohort	Multi-center	Etiology	Death attributed to fatal arrhythmias, hypertensive heart disease, cardiomyopathies, arterial disease, heart failure, and pulmonary embolism.	No
Van Adrichem, 2017 [92]	3,062	RCT	Multi-center	Prevention	VTE	Yes
Van der Hulle, 2017 [93]	3,465	Prospective cohort	Multi-center	Diagnosis	VTE	Yes
Van Es, 2018 [94]	117	Prospective cohort	Multi-center	Prediction	VTE	Yes
Vanni, 2015 [95]	496	Prospective cohort	Multi-center	Prediction	Composite of PE-related death or non-fatal haemodynamic collapse	Yes
Wahlsten, 2015 [96]	57,619	Retrospective cohort	Multi-center	Incidence	Hospitalization for VTE or death from PE	No

Study	Sample size	Design	Centers	Study type	Primary outcome	Adjudication committee
Walker, 2016 [97]	10,598	Retrospective cohort	Multi-center	Incidence	VTE	No
Weitz, 2017 [98]	3,365	RCT	Multi-center	Treatment	Recurrent VTE	Yes
Yamada, 2015 [99]	100	RCT	Multi-center	Treatment	Recurrent VTE and asymptomatic deterioration	Yes
Zahir, 2017 [100]	400	Retrospective cohort	Single center	Incidence	VTE	No

Abbreviations: DVT: deep vein thrombosis, PE: pulmonary embolism, RCT: randomized clinical trial, VTE: venous thromboembolism

Table 2 – Components of the definitions for pulmonary embolism-related death

Study	**Components of the definitions for pulmonary embolism-related death**
Abbasi, 2011 [19]	-
Ageno, 2016 [20]	-
Al-Hameed, 2014 [21]	-
Alatri, 2017 [22]	Death following VTE for which VTE was judged to be the cause of death
Allen, 2015 [23]	-
Andreozzi, 2015 [24]	Objectively confirmed PE on imaging before death
Apenteng, 2017 [25]	-
Assareh, 2014 [26]	-
Bahl, 2014 [27]	-
Bayley, 2016 [28]	-
Becattini, 2016 [29]	• Autopsy-confirmed PE • Objectively confirmed PE before death • Sudden death in the absence of a more probable cause of death
Bedayat, 2015 [30]	• Autopsy-confirmed PE • Specific signs or symptoms before death in the absence of other cardiopulmonary diseases
Blix, 2018 [31]	-

Study	Components of the definitions for pulmonary embolism-related death
Bogdan, 2014 [32]	-
Bouras, 2015 [33]	-
Bova, 2018 [34]	• Objective documentation of PE • Unexplained death for which PE cannot be ruled out
Büller, 2015 [35]	• Autopsy-confirmed PE • Objectively confirmed PE before death • Unexplained death for which PE cannot be ruled out
Camporese, 2016 [36]	• Autopsy-confirmed PE • On clinical grounds according to the treating physician's judgment
Catterick, 2014 [37]	-
Ciurzynski, 2018 [38]	-
Cohen, 2016 [39]	-
Couturaud, 2015 [40]	• Autopsy-confirmed PE • Objectively confirmed PE on imaging before death • Sudden death for which PE cannot be ruled out
Den Exter, 2016 [41]	-
Etesamifard, 2016 [42]	Death occurring within 30 days after PE
Fernandez, 2015 [43]	• Objective documentation of PE • Unexplained death for which PE cannot be ruled out
Font, 2014 [44]	-

Study	Components of the definitions for pulmonary embolism-related death
Freund, 2018 [45]	Sudden death in the absence of another obvious cause of death
Gaertner, 2017 [46]	Other causes of death are excluded and PE cannot be ruled out
George, 2014 [47]	• Autopsy-confirmed PE • Specific signs or symptoms before death in the absence of other cardiopulmonary diseases
Gladman, 2014 [48]	-
Hara, 2017 [49]	• Objective documentation of PE • No other documented cause of death and PE cannot be ruled out
Horner, 2014 [50]	-
Horner, 2014 [51]	-
Im, 2017 [52]	Objectively confirmed PE soon before death in the absence of an alternative diagnosis
Imberti, 2014 [53]	-
Izumi, 2015 [54]	-
Jimenez-Alcazar, 2018 [55]	• Autopsy-confirmed PE • Objectively confirmed clinically severe PE before death • Sudden or unexpected death for which PE cannot be ruled out
Johansson, 2018 [56]	Autopsy-confirmed PE
Kawaguchi, 2017 [57]	-
Kline, 2014 [58]	Death within 5 days of PE

Study	Components of the definitions for pulmonary embolism-related death
Koc, 2016 [59]	• Objectively confirmed PE before death • Specific signs or symptoms before death in the absence of an alternative cause of death
Kolluri, 2016 [60]	-
Krause, 2016 [61]	-
Kumamaru, 2016 [62]	• Autopsy-confirmed PE • Specific signs or symptoms before death in the absence of other cardiopulmonary diseases
Lankeit, 2014 [63]	• Autopsy-confirmed PE • Objectively confirmed clinically severe PE before death in the absence of an alternative diagnosis
Lee, 2015 [64]	• Autopsy-confirmed PE • Objectively confirmed PE on imaging before death • Sudden and unexplained death for which PE cannot be ruled out
Li, 2015 [65]	Objectively confirmed in the 30 days before death in the absence of another cause of death
Marconi, 2016 [66]	-
Migita, 2014 [67]	-
Mismetti, 2015 [68]	• Autopsy-confirmed PE • Objectively confirmed PE on imaging before death • Unexplained death for which PE cannot be ruled out
Moores, 2016 [69]	• Autopsy-confirmed PE • Objectively confirmed clinically severe PE before death • Sudden or unexplained death
Mos, 2014 [70]	• Objectively confirmed PE before death • Death for which PE cannot be ruled out

Study	Components of the definitions for pulmonary embolism-related death
Nendaz, 2014 [71]	• Autopsy-confirmed PE • Objectively confirmed PE on imaging before death • Death in which VTE was considered a likely contributor to the fatal outcome
Obi, 2015 [72]	-
Ogonda, 2016 [73]	-
Onundarson, 2015 [74]	-
Paczynska, 2016 [75]	-
Pruszczyk, 2014 [76]	-
Raskob, 2018 [17]	• Objective documentation that PE caused the death • No other documented cause of death and PE cannot be ruled out
Ratib, 2016 [77]	-
Reitter, 2016 [78]	-
Roy, 2017 [79]	-
Roy, 2016 [80]	-
Ryan, 2015 [81]	-
Sakai, 2016 [82]	-
Samama, 2014 [83]	-

Study	Components of the definitions for pulmonary embolism-related death
Selby, 2014 [84]	• Autopsy-confirmed PE • Sudden, unexplained death in patients without an autopsy
Selby, 2015 [85]	• Autopsy-confirmed PE • Sudden, unexplained death in patients without an autopsy
Shirakawa, 2016 [86]	-
Suttorp, 2014 [87]	-
Tafur, 2017 [88]	Death within 10 days of a VTE event in the absence of an alternative cause of death
Tanaka, 2015 [89]	• Autopsy confirmed VTE • Objectively confirmed VTE by imaging • Death related to VTE based on physician's judgment
Tapson, 2017 [90]	• Death caused by PE • Unexpected death within 24 hours of onset of the acute PE event
Twig, 2017 [91]	-
Van Adrichem, 2017 [92]	-
Van der Hulle, 2017 [93]	• Autopsy-confirmed PE • Objectively confirmed PE before death • Death for which PE cannot be ruled out
Van Es, 2018 [94]	-
Vanni, 2015 [95]	• Objective documentation of PE • Unexplained death for which PE cannot be ruled out
Wahlsten, 2015 [96]	-

Study	Components of the definitions for pulmonary embolism-related death
Walker, 2016 [97]	-
Weitz, 2017 [98]	• Autopsy-confirmed PE • Objectively confirmed PE before death • Unexplained death for which PE cannot be ruled out
Yamada, 2015 [99]	• Objective documentation of PE • Unexplained death for which PE cannot be ruled out
Zahir, 2017 [100]	• Fatal PE as judged by the primary physician • Sudden or unexplained death in the presence of specific signs or symptoms

Abbreviations: PE: pulmonary embolism, VTE: venous thromboembolism.

Table 3 – Outcome event rates reported in the included studies

Study	Sample size, n	(Recurrent) VTE, n	All-cause mortality, n	PE-related death, n	Case-fatality rate VTE events* (%)	Death due to PE rate** (%)
Abbasi, 2011 [19]	8,826,439	14,741	746	61	0.41	8.2
Ageno, 2016 [20]	5,142	92	100	10	11	10
Al-Hameed, 2014 [21]	147	147	16	16	11	100
Alatri, 2017 [22]	383	-	-	-	-	-
Allen, 2015 [23]	5,809	112	3	2	1.8	67
Andreozzi, 2015 [24]	617	45	4	1	2.2	25
Apenteng, 2017 [25]	1,011	21	246	3	14	1.2
Assareh, 2014 [26]	4,223,317	8,451	-	673	8.0	-
Bahl, 2014 [27]	3,498	45	-	-	-	-
Bayley, 2016 [28]	7,983	N/A	-	6	N/A	-
Becattini, 2016 [29]	906	N/A	65	37	N/A	57
Bedayat, 2015 [30]	1,664	N/A	327	109	N/A	33
Blix, 2018 [31]	14,272	2,444	-	-	-	-

Study	Sample size, n	(Recurrent) VTE, n	All-cause mortality, n	PE-related death, n	Case-fatality rate VTE events* (%)	Death due to PE rate** (%)
Bogdan, 2014 [32]	312	15	-	12	80	-
Bouras, 2015 [33]	159,039	981	2,426	116	12	4.8
Bova, 2018 [34]	639	N/A	34	9	N/A	26
Büller, 2015 [35]	300	60	0	0	0	0
Camporese, 2016 [36]	241	10	0	0	0	0
Catterick, 2014 [37]	-	-	-	-	-	-
Ciurzynski, 2018 [38]	400	N/A	15	6	N/A	40
Cohen, 2016 [39]	7,513	388	425	41	11	9.7
Couturaud, 2015 [40]	371	28	19	0	0	0
Den Exter, 2016 [41]	550	5	7	1	20	14
Etesamifard, 2016 [42]	203	N/A	11	9	N/A	82
Fernandez, 2015 [43]	1,083	N/A	176	44	N/A	25
Font, 2014 [44]	138	N/A	32	5	N/A	16
Freund, 2018 [45]	1,916	41	5	0	0	0

Study	Sample size, n	(Recurrent) VTE, n	All-cause mortality, n	PE-related death, n	Case-fatality rate VTE events* (%)	Death due to PE rate** (%)
Gaertner, 2017 [46]	499	15	24	5	33	21
George, 2014 [47]	785	N/A	104	36	N/A	35
Gladman, 2014 [48]	50	4	15	0	0	0
Hara, 2017 [49]	53	0	12	0	0	0
Horner, 2014 [50]	212	1	1	0	0	0
Horner, 2014 [51]	70	1	0	0	0	0
Im, 2017 [52]	172	N/A	27	23	N/A	85
Imberti, 2014 [53]	258	3	0	0	0	0
Izumi, 2015 [54]	1,288	312	0	-	-	-
Jimenez-Alcazar, 2018 [55]	611	70	129	9	13	7.0
Johansson, 2018 [56]	108,025	2,054	-	-	-	-
Kawaguchi, 2017 [57]	295	0	0	-	-	-
Kline, 2014 [58]	83	N/A	2	1	N/A	50
Koc, 2016 [59]	138	N/A	34	26	N/A	76

Study	Sample size, n	(Recurrent) VTE, n	All-cause mortality, n	PE-related death, n	Case-fatality rate VTE events* (%)	Death due to PE rate** (%)
Kolluri, 2016 [60]	78	2	0	0	0	0
Krause, 2016 [61]	212	2	-	0	0	-
Kumamaru, 2016 [62]	579	N/A	-	6	N/A	-
Lankeit, 2014 [63]	688	N/A	29	18	N/A	62
Lee, 2015 [64]	900	76	288	34	45	12
Li, 2015 [65]	71	N/A	7	5	N/A	71
Marconi, 2016 [66]	471	34	109	13	38	12
Migita, 2014 [67]	2,162	314	0	0	0	0
Mismetti, 2015 [68]	399	14	36	9	64	25
Moores, 2016 [69]	134	2	5	0	0	0
Mos, 2014 [70]	516	8	22	1	13	4.6
Nendaz, 2014 [71]	1,478	30	-	18	60	-
Obi, 2015 [72]	4,844	387	-	-	-	-
Ogonda, 2016 [73]	11,459	151	45	8	5.3	18

Study	Sample size, n	(Recurrent) VTE, n	All-cause mortality, n	PE-related death, n	Case-fatality rate VTE events* (%)	Death due to PE rate** (%)
Onundarson, 2015 [74]	1,156	29	28	-	-	-
Paczynska, 2016 [75]	76	N/A	10	8	N/A	80
Pruszczyk, 2014 [76]	411	N/A	21	14	N/A	67
Raskob, 2018 [17]	1,050	100	398	6	6.0	1.5
Ratib, 2016 [77]	3,558,680	108,770	-	-	-	-
Reitter, 2016 [78]	112	14	22	0	0	0
Roy, 2017 [79]	1,081	-	-	-	-	-
Roy, 2016 [80]	15,351	278	1704	139	50	8.2
Ryan, 2015 [81]	24	2	-	0	0	-
Sakai, 2016 [82]	120	29	-	0	0	-
Samama, 2014 [83]	1,349	63	1	0	0	0
Selby, 2014 [84]	1,200	7	-	0	0	-
Selby, 2015 [85]	265	5	-	0	0	-
Shirakawa, 2016 [86]	86,024	N/A	-	59	N/A	-

Study	Sample size, n	(Recurrent) VTE, n	All-cause mortality, n	PE-related death, n	Case-fatality rate VTE events* (%)	Death due to PE rate** (%)
Suttorp, 2014 [87]	805	13	-	-	-	-
Tafur, 2017 [88]	7,948	418	2,229	54	13	2.4
Tanaka, 2015 [89]	184	N/A	184	13	N/A	7.1
Tapson, 2017 [90]	163	0	25	0	0	0
Twig, 2017 [91]	2,294,139	N/A	32,127	70	N/A	0.22
Van Adrichem, 2017 [92]	3,062	31	1	0	0	0
Van der Hulle, 2017 [93]	3,465	18	98	6	33	6.1
Van Es, 2018 [94]	117	11	31	2	18	6.5
Vanni, 2015 [95]	496	N/A	27	12	N/A	44
Wahlsten, 2015 [96]	57,619	594	-	8	1.4	-
Walker, 2016 [97]	10,598	364	-	-	-	-
Weitz, 2017 [98]	3,365	80	17	4	5.0	24
Yamada, 2015 [99]	100	1	3	0	0	0
Zahir, 2017 [100]	400	42	-	1	2.4	-

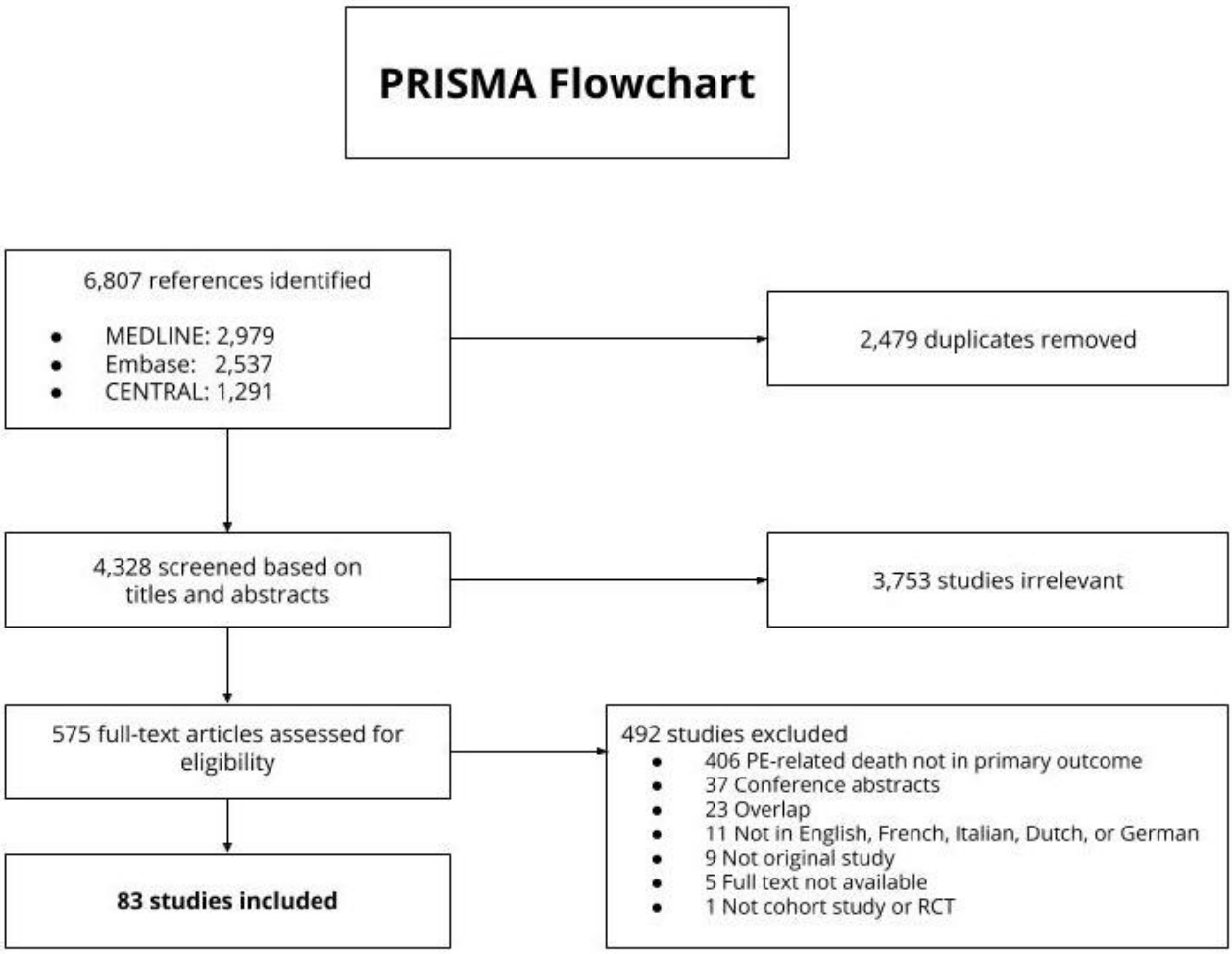
Abbreviations: N/A: not applicable, PE: pulmonary embolism, VTE: venous thromboembolism.

* The case-fatality rate is the proportion of (recurrent) venous thromboembolic events that were fatal.

** The death due to PE rate is the proportion of deaths that were attributable to PE.

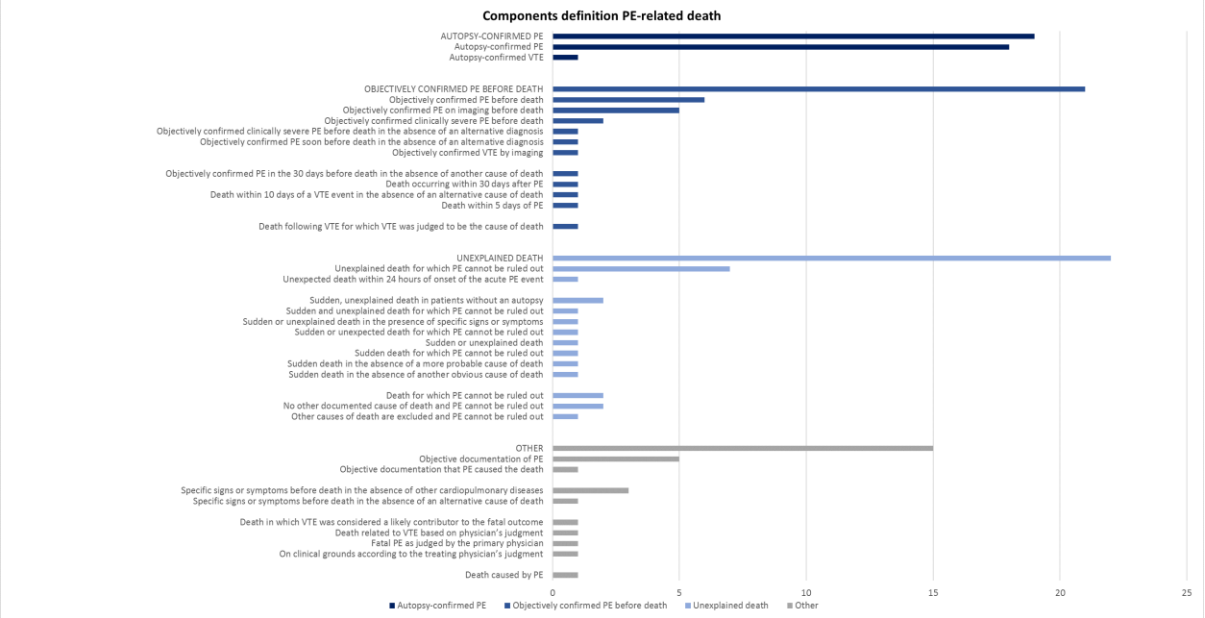
FIGURES

Figure 1 – PRISMA flowchart



Shown is the PRISMA flowchart indicating the process for the selection of eligible studies.

Figure 2 – Frequencies of the components included in the definitions for pulmonary embolism-related death



Shown are the frequencies of the components used to define PE-related death in the included studies. Components were classified into four categories: 'Autopsy-confirmed PE' (n=19), 'Objectively confirmed PE before death' (n=21), 'Unexplained death' (n=22), and 'Other' (n=15). For each category, the bar at the top represents the total number of studies that included the component subgroup in the definition for PE-related death. The bars below indicate the frequencies for each of the variations used to describe that component subgroup.

APPENDICES

Appendix 1 - Electronic search strategies

Database: Ovid MEDLINE(R) ALL <1946 to April 26, 2018>
Search Strategy:

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1 venous thromboembolism/ or venous thromboembolism.tw. (18655)
2 Venous Thrombosis/ or ((venous or vein) adj3 thrombo*).tw. (68083)
3 Pulmonary Embolism/ or ((pulmonary or lung) adj3 emboli*).tw. (50001)
4 or/1-3 (104458)
5 FATAL OUTCOME/ (58610)
6 (fatal or death).tw. (692884)
7 MORTALITY/ (39556)
8 mortality.tw,kw. (642835)
9 or/5-8 (1266725)
10 4 and 9 (17568)
11 cohort studies/ or prospective studies/ or retrospective studies/ (1272010)
12 (cohort or prospective* or retrospective*).tw. (1382200)
13 randomized controlled trial.pt. (459658)
14 controlled clinical trial.pt. (92364)
15 randomi?ed.ab. (490388)
16 placebo.ab. (188521)
17 clinical trials as topic.sh. (183424)
18 randomly.ab. (289382)
19 trial.ti. (181508)
20 or/11-19 (2780663)
21 10 and 20 (7153)
22 *venous thromboembolism/ or venous thromboembolism.ti. (11211)
23 *Venous Thrombosis/ or ((venous or vein) and thrombo*).ti. (39179)
24 *Pulmonary Embolism/ or ((pulmonary or lung) and (emboli* or thrombo*)).ti. (31195)
25 or/22-24 (68058)
26 randomized controlled trial.pt. (459658)
27 controlled clinical trial.pt. (92364)
28 randomi?ed.ab. (490388)
29 or/26-28 (786502)
30 25 and 29 (3703)
31 21 or 30 (9923)
32 limit 31 to yr="2014 -Current" (3027)
33 (child/ or infant/) not adult/ (1254860)
34 32 not 33 (2979)

Database: Embase Classic+Embase <1947 to 2018 April 26>
Search Strategy:

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1 *deep vein thrombosis/ (15211)
2 *lung embolism/ (33096)
3 *vein thrombosis/ (15101)
4 *thromboembolism/ (20077)
5 *venous thromboembolism/ (13410)
6 ((venous or vein) and thrombo*).ti. (45763)
7 ((pulmonary or lung) and (emboli* or thrombo*)).ti. (30580)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (108006)
9 *fatality/ or *mortality/ (87735)
10 (fatal* or death or mortality).tw. (1799286)
11 9 or 10 (1810431)
12 8 and 11 (17313)
13 *cohort analysis/ (17553)
14 *retrospective study/ (12595)
15 *prospective study/ (14202)
16 (cohort or prospective* or retrospective*).tw. (2168890)
17 major clinical study/ (3093727)
18 random:.tw. (1307150)
19 placebo:.mp. (422474)
20 double-blind:.tw. (192222)
21 or/13-20 (5496658)
22 12 and 21 (8974)
23 *venous thromboembolism/ or *vein thrombosis/ or ((venous or vein) adj3 thrombo*).ti. (51878)
24 *lung embolism/ or ((pulmonary or lung) adj3 emboli*).ti. (34887)
25 23 or 24 (82629)
26 random:.tw. (1307150)
27 placebo:.mp. (422474)
28 double-blind:.tw. (192222)
29 26 or 27 or 28 (1559424)
30 25 and 29 (5943)
31 22 or 30 (13151)
32 limit 31 to yr="2014 -Current" (4533)
33 (exp infant/ or exp child/ or adolescent/) not exp adult/ (2229776)
34 32 not 33 (4440)
35 limit 34 to (conference abstract or conference paper) (1903)
36 34 not 35 (2537)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <March 2018>
Search Strategy:

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1 venous thromboembolism/ or venous thromboembolism.tw. (2016)
2 Venous Thrombosis/ or ((venous or vein) adj3 thrombo*).tw. (6106)
3 Pulmonary Embolism/ or ((pulmonary or lung) adj3 emboli*).tw. (2410)
4 or/1-3 (7177)
5 FATAL OUTCOME/ (12)
6 (fatal or death).tw. (33725)
7 MORTALITY/ (430)
8 mortality.tw,kw. (42003)
9 or/5-8 (65892)
10 4 and 9 (1346)
11 *venous thromboembolism/ or venous thromboembolism.ti. (1162)
12 *Venous Thrombosis/ or ((venous or vein) and thrombo*).ti. (3522)
13 *Pulmonary Embolism/ or ((pulmonary or lung) and (emboli* or thrombo*)).ti. (814)
14 or/11-13 (4255)
15 10 or 14 (4953)
16 limit 15 to yr="2014 -Current" (1291)

Appendix 2 – Definitions for pulmonary embolism-related death as reported in the original studies

Study	Definition PE-related death
Abbasi, 2011	-
Ageno, 2016	-
Al-Hameed, 2014	-
Alatri, 2017	Death following VTE in which VTE was considered a likely contributor to the fatal outcome.
Allen, 2015	-
Andreozzi, 2015	Fatal PE objectively confirmed by computed tomography or lung scanning.
Apenteng, 2017	-
Assareh, 2014	-
Bahl, 2014	-
Bayley, 2016	-
Becattini, 2016	PE was considered the cause of death based on the autopsy or objective testing performed before death or in case of sudden death that could not be explained by a more compelling alternative diagnosis.
Bedayat, 2015	Death was considered PE-related when (1) either the autopsy data, death certificate, or death report on the electronic medical record identified PE-related death or (2) acute respiratory failure, cardiopulmonary arrest, or shock was the cause of death, in the absence of other cardiopulmonary diseases.
Blix, 2018	-
Bogdan, 2014	-
Bouras, 2015	-
Bova, 2018	PE was considered the cause of death if there was objective documentation or in case of unexplained death and PE not confidently ruled out.
Büller, 2015	PE based on objective diagnostic testing, autopsy, or death which cannot be attributed to a documented cause and for which PE/DVT cannot be ruled out (unexplained death).
Camporese, 2016	Fatal PE was diagnosed by autopsy, or on clinical grounds according to the treating physician judgment.
Catterick, 2014	-
Ciurzynski, 2018	-
Cohen, 2016	-

Study	Definition PE-related death
Couturaud, 2015	Recurrent VTE was defined as fatal in cases of death caused by VTE diagnosed according to the above criteria: objectively confirmed on imaging, autopsy confirmed or sudden death for which no other cause could be identified (recurrent pulmonary embolism could not be ruled out by the Critical Events Committee).
Den Exter, 2016	-
Etesamifard, 2016	PE-related death (death occurring within 30 days after presentation).
Fernandez, 2015	PE was considered the cause of death if there was objective documentation or the cause was unexplained and PE could not be confidently ruled out.
Font, 2014	-
Freund, 2018	A sudden death in the absence of another obvious cause will be adjudicated as related to a PE.
Gaertner, 2017	Recurrent VTE was considered as the cause of death when other causes were excluded and when PE could not be ruled out.
George, 2014	A subject was considered to have died of PE-related causes if (a) the autopsy report, death certificate, or electronic medical record stated PE as a cause of death, or (b) respiratory failure, cardiopulmonary arrest, or shock was the immediate cause of death in the absence of other cardiopulmonary diseases or precipitating factors.
Gladman, 2014	-
Hara, 2017	PE was considered the cause of death if there was objective documentation or if death could not be attributed to any other documented cause and PE could not be excluded.
Horner, 2014	-
Horner, 2014 (RCT)	-
Im, 2017	PE-related death was defined as death soon after objective confirmation of symptomatic PE in the absence of any alternative diagnosis.
Imberti, 2014	-
Izumi, 2015	-
Jimenez-Alcazar, 2018	Death was PE-related if PE was confirmed by autopsy, or if death followed a clinically severe PE, either initially or after an objectively confirmed recurrent event. Death in a patient who died suddenly or unexpectedly was classified as possibly PE-related.
Johansson, 2018	Participants who had a VTE event registered as the main cause of death and who underwent autopsy were regarded as having a verified VTE.
Kawaguchi, 2017	-
Kline, 2014	Death within 5 days of PE.
Koc, 2016	PE-related mortality was diagnosed when haemodynamic instability and/or shock preceded death, or when a patient experienced pulmonary embolism recurrence. When an evident alternative cause of death was reported, such as severe bleeding, neoplasm or sepsis with no data for PE-related death, a non-PE death was diagnosed and

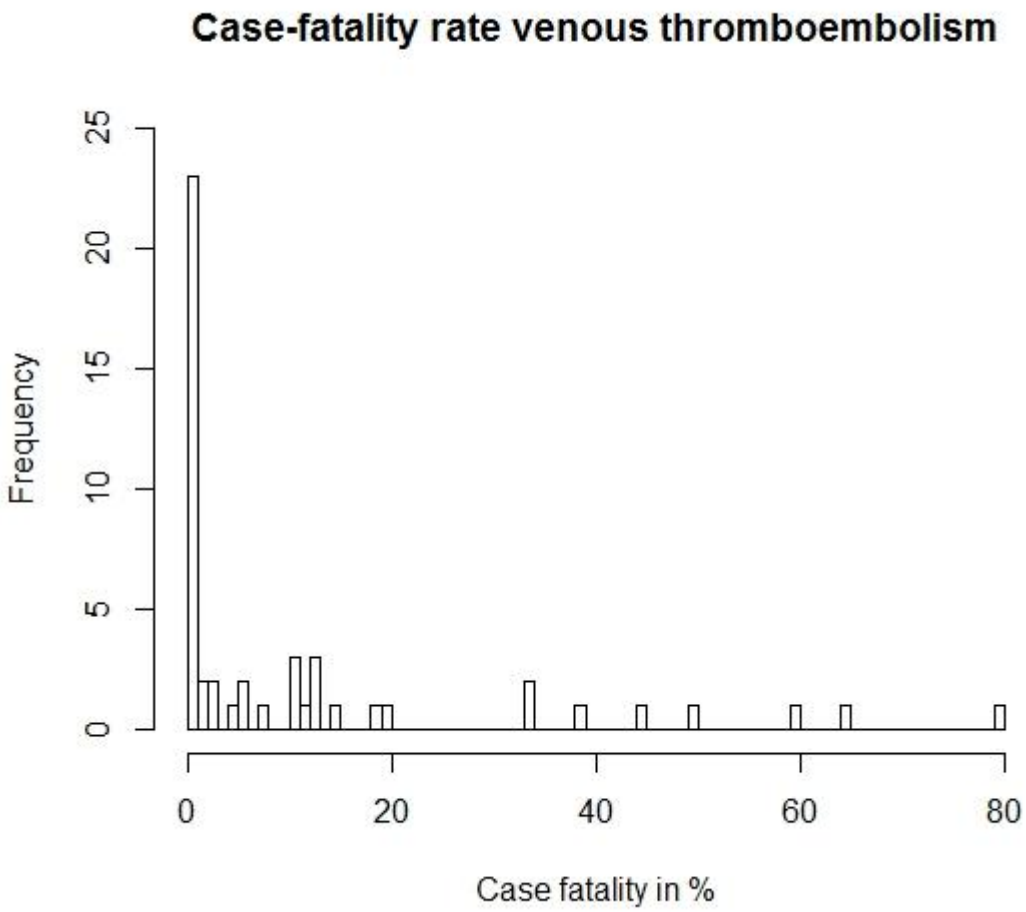
Study	Definition PE-related death
	this contributed to 30-day all-cause mortality.
Kolluri, 2016	-
Krause, 2016	-
Kumamaru, 2016	Death was considered as PE-related by consensus of three physicians, when (1) either the autopsy data, death certification, or death report on the electronic medical record stated that the death was caused by PE; or (2) acute respiratory failure, cardiopulmonary arrest or shock was the cause of death, in the absence of other cardiopulmonary disease.
Lankeit, 2014	Death was determined to be related to PE if it was confirmed by autopsy, or if it followed a clinically severe PE episode, either immediately or shortly after an objectively confirmed recurrent event, and in the absence of an alternative diagnosis.
Lee, 2015	Fatal PE was defined as proven on objective imaging, autopsy, or as the most probable cause of a sudden and unexplained death according to central adjudication.
Li, 2015	A patient was considered to have died from PE if death occurred within 30 days of PE diagnosis and was not attributed to a specific cause aside from PE.
Marconi, 2016	-
Migita, 2014	-
Mismetti, 2015	PE-related death was not explicitly defined. However, it was included in the definition of recurrent PE: Symptomatic PE recurrence confirmed by lung scan and/or spiral CT scan and/or pulmonary angiography, fatal PE confirmed at autopsy, or unexplained death for which a causative role of PE cannot be ruled out.
Moores, 2016	Fatal PE was classified as definitely present if PE was confirmed by autopsy, or if death followed a clinically severe PE. Fatal PE was classified as possibly present in patients who died suddenly or unexpectedly.
Mos, 2014	Death was classified as due to PE in case of objective confirmation of PE prior to death or if PE could not be confidently excluded as the cause of death.
Nendaz, 2014	Death following VTE, confirmed by autopsy or an imaging test, or death in which VTE was considered a likely contributor to the fatal outcome.
Obi, 2015	-
Ogonda, 2016	-
Onundarson, 2015	-
Paczynska, 2016	-
Pruszczyk, 2014	-
Raskob, 2018	PE was considered to be the cause of death if there was objective documentation that pulmonary embolism caused the death or if the death could not be attributed to a documented cause and pulmonary embolism could not be ruled out.

Study	Definition PE-related death
Ratib, 2016	-
Reitter, 2016	-
Roy, 2017	-
Roy, 2016	-
Ryan, 2015	-
Sakai, 2016	-
Samama, 2014	-
Selby, 2014	Fatal PE was defined as autopsy-proven pulmonary embolism; possible fatal PE was defined as an otherwise unexplained sudden death of a patient without an autopsy.
Selby, 2015	Fatal PE was defined as autopsy-proven PE; possible fatal PE was defined as otherwise unexplained, sudden death in patients without an autopsy.
Shirakawa, 2016	-
Suttorp, 2014	-
Tafur, 2017	Fatal VTE was defined as any death occurring within 10 days of a corresponding event, in the absence of an alternative cause of death.
Tanaka, 2015	Maternal-death-related VTE was defined as VTE demonstrated by contrast enhanced computed tomography, pulmonary arteriography, lung scintigraphy, ultrasound sonography, autopsy imaging, and/or autopsy, and either a number of expert obstetricians in the Maternal Death Exploratory Committee (2010–2013) or Nagaya's group (1991–1992) judging VTE as the cause of death.
Tapson, 2017	Fatal PE was defined as death caused by PE or unexpected death within 24 hours of onset of the acute event.
Twig, 2017	-
Van Adrichem, 2017	-
Van der Hulle, 2017	Deaths were classified as caused by PE if it was confirmed by autopsy, was shown by objective testing before death, or could not be confidently excluded as a cause of death.
Van Es, 2018	-
Vanni, 2015	PE was considered the cause of death if there was objective documentation or if the cause was unexplained and PE could not be confidently ruled out.
Wahlsten, 2015	-
Walker, 2016	-

Study	Definition PE-related death
Weitz, 2017	Fatal PE based on autopsy or objective diagnostic testing prior to death. Death that could not be attributed to a documented cause and for which PE/DVT could not be ruled out (unexplained death).
Yamada, 2015	PE was considered as the cause of death if there was objective documentation, or if death could not be attributed to a documented cause and PE could not be ruled out.
Zahir, 2017	Cause of death/morbidity defined as PE by primary physician and for patients who develop signs and symptoms of VTE but died before diagnostic criteria could be met, sudden, otherwise unexplained death was taken as a VTE event in the presence of severe hypoxia on arterial blood gases and no acute change in chest X-ray.

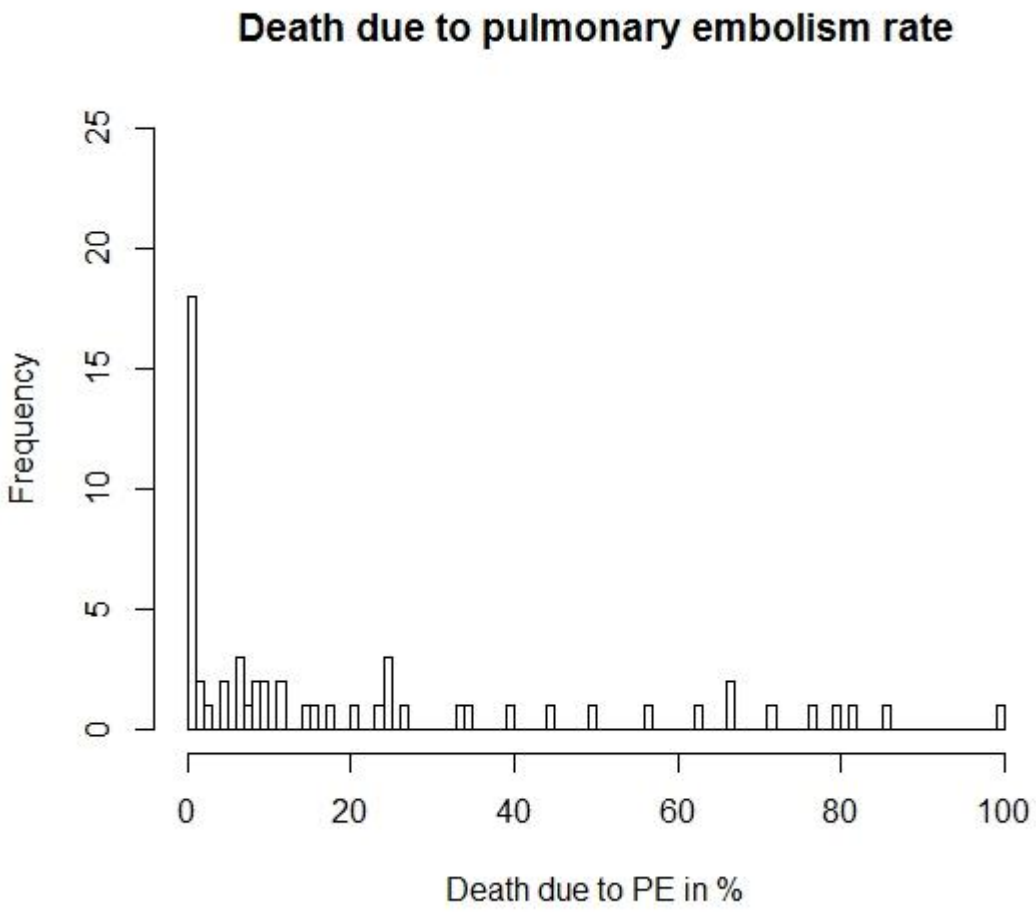
Abbreviations: DVT: deep vein thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism.

Appendix 3 – Case-fatality rate of venous thromboembolism



Shown are the frequencies of the case-fatality rates of venous thromboembolism reported in the included studies, defined as the proportion of venous thromboembolic events that were fatal. Median case-fatality rate of venous thromboembolism was 1.8% (IQR, 0.0 to 13).

Appendix 4 – Death due to pulmonary embolism rate



Shown are the frequencies of the death due to pulmonary embolism rates reported in the included studies, defined as the proportion of death events that were attributable to pulmonary embolism. Median death due to pulmonary embolism rate was 8.2% (IQR, 0.0 to 33).